

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
5 July 2001 (05.07.2001)

PCT

(10) International Publication Number  
**WO 01/47503 A1**

- (51) International Patent Classification<sup>7</sup>: **A61K 9/70**, (74) Agent: **PHARMACIA AB**; Box 941, S-251 09 Helsingborg (SE).  
31/5375, A61P 25/24
- (21) International Application Number: **PCT/SE00/01972** (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: 12 October 2000 (12.10.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 9904750-8 23 December 1999 (23.12.1999) SE
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (for all designated States except US): **PHARMACIA AB** [SE/SE]; S-112 87 Stockholm (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HOECK, Ulla** [DK/DK]; Kighusvaenget 7, DK-3400 Hillerød (DK). **KREILGÅRD, Bo** [DK/DK]; Smedievej 18, DK-3400 Hillerød (DK). **KRISTENSEN, Helle** [DK/DK]; Lindegårds Allé 16, DK-3550 Slangerup (DK).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **TRANSDERMAL ADMINISTRATION OF REBOXETINE**

(57) Abstract: Device for transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, to the use of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, method for the manufacturing of a medicament to be administered transdermally, and methods of treating depression and/or symptoms associated with this condition and/or for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome and symptoms associated with these conditions, and/or for obtaining an anti-reserpine and/or noradrenaline reuptake inhibiting effect by transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof.

Transdermal administration of Reboxetine

---

**Field of invention**

This invention relates to a device for transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, to the use of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, for the manufacturing of a medicament to be administered transdermally, and to methods of treating depression and/or symptoms associated with this condition and/or for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome and symptoms associated with said conditions, and/or for obtaining an anti-reserpine and/or noradrenaline reuptake inhibiting effect by transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof.

**Background**

Reboxetine is the generic name of the pharmaceutical substance having the chemical name 2-( $\alpha$ -(2-ethoxyphenoxy)benzyl)-morpholine and its pharmaceutically acceptable salts. Reboxetine can be a free base, or it can include reboxetine methanesulfonate (also called reboxetine mesylate) or any other pharmaceutically acceptable salt that does not significantly affect the pharmaceutical activity of the substance. Reboxetine and a method of synthesis thereof are described in US 4,229,449. Methods of preparation are described in US 5,068,433 and US 5,391,735. Reboxetine is also known under the trade name EDRONAX®.

Reboxetine is a selective and potent inhibitor of the reuptake of noradrenaline; it also has a weak effect on serotonin reuptake. Pharmacodynamic studies performed in vivo and in vitro indicate that reboxetine possesses antidepressant activity and a lower

incidence of side effects than commonly is seen with the tricyclic antidepressants. Reboxetine is highly potent, with central nervous system (CNS) effects demonstrated at doses of 1 and 3 mg. Phase II studies in patients with Major Depressive Disorders identified the non-tolerated dose in patients as 12 mg/day, which produced dose-limiting  
5 hypotension. Therefore, daily doses of 8 and 10 mg were selected for subsequent development, since these doses were associated with maximal response and minimal side-effects.

Pharmacokinetic studies of reboxetine indicate that the drug is rapidly and extensively absorbed after oral administration. Soon after peak plasma levels are obtained  
10 reboxetine plasma levels decay with a half-life of 12-16 hours. Unchanged drug, extensively bound to plasma proteins, is the main molecular species that is present in the systemic circulation. Clearance from the systemic circulation is mainly taking place by hepatic metabolism. The amount excreted by the renal pathway accounted for 78 % of the administered dose, of which 13 % was unchanged reboxetine.

15 Reboxetine is an equimolar mixture of two enantiomers. The pharmacokinetics of each enantiomer have been evaluated, and neither chiral inversion nor interactions between enantiomers have been observed after racemic administration.

Reboxetine has a molecular weight of 313,4 g/mol and 409,5 g/mol as the methanesulphonate salt. Reboxetine base is freely soluble in ethanol, propylene glycol,  
20 ethylacetate and isopropylmyristate. It is slightly soluble in water and 0,05 M phosphate buffer, pH 7,4. The partition coefficient (Log P) between n-octanol and phosphate buffer at pH 7,4 is 0,86.

The present invention pertains to transdermal administration of reboxetine as R-isomer, S-isomer or as a racemic mixture. Properties supporting the feasibility of the  
25 patch principle are that depression and symptoms associated with this condition, as well as with the other conditions mentioned above, might benefit from a flat serum concentration profile.

### **Prior Art**

WO 99/11208 (Williams and Murdock) discloses transdermal delivery of a large  
30 number of medical agents, including reboxetine, using a matrix of a lecithin gel such as a lecithin organogel. However, WO 99/11208 does not disclose transdermal delivery of reboxetine from any other transdermal system.

A number of publications disclose different devices for transdermal administration of drugs as such. Except for the captioned WO 99/11208 no such publication

though relates to transdermal delivery of reboxetine. For example US 5 811 465 discloses transdermal delivery of anti-depressive compounds, without relating at all to reboxetine.

### **Objects of the invention**

5 A transdermal formulation with reboxetine as active ingredient will provide an alternative to the tablet formulation for the oral route. The possibility exists that due to the more constant serum concentrations during a dosage interval, side effects in comparison to immediate release tablets may be further reduced, while clinical efficacy is maintained.

10 The transdermal delivery route avoids the risk for dose dumping with extended release oral forms of administration. Moreover, patient compliance will be increased as

- elderly people and children may have difficulties in swallowing oral dosage forms,

- patients may visually observe that they are taking their medication (contrary to

15 not remembering whether they swallowed their tablet),

- once-a-day administration is possible,

- several-days administration is possible with one patch.

Overall, these effects increase convenience and compliance for patients.

Accordingly, a first object of the present invention is to provide a device for

20 transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, for achieving an antidepressant effect and/or for obtaining an effect in treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders,

25 bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-

30 traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

A second object of the invention is to provide a device for transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, for achieving an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect.

A third object of the invention is to provide use of a compound having an anti-depressant effect, comprising reboxetine for the manufacture of a composition to be administered transdermally for treating depression or symptoms associated with this condition and/or for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome.

A fourth object of the invention is to provide use of a compound having an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect, comprising reboxetine for the manufacture of a composition to be administered transdermally for treating conditions in need for such effects.

A fifth object of the invention is to provide a method of treating depression or symptoms associated with this condition and/or for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder,

der, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome by administering reboxetine transdermally.

A sixth object of the invention is to provide a method of treating diseases, in humans or animals, which are treatable with anti-reserpine agents and/or noradrenaline uptake inhibiting agents by administering reboxetine transdermally.

Other objects of the invention will become apparent to one skilled in the art, and still other objects will become apparent hereinafter.

#### **Summary of the invention**

The present invention relates to transdermal administration of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof for achieving an antidepressant effect and/or an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect. Said effects are primarily achieved through the systemic effect of reboxetine. Anyhow other actions are not excluded.

#### **Brief description of the drawings**

Figures 1A – 1D are schematic drawings of different types of devices for transdermal delivery of drugs.

Figure 2 is a diagram showing *in vitro* skin permeation of reboxetine base from saturated solutions, according to Example 1.

Figure 3 is a diagram showing *in vitro* skin permeation of 5 % reboxetine base solutions, according to Example 2 and Example 3.

Figure 4 is a diagram showing *in vitro* skin permeation across synthetic membranes from 5 % reboxetine base solutions, according to Example 4.

Figure 5 is a diagram showing *in vitro* skin permeation of reboxetine base from different transdermal systems, according to Example 6.

Figure 6 is a diagram showing *in vitro* skin permeation of reboxetine base from different transdermal systems, applying human skin, according to Example 7.

Figures 7 and 8 are diagrams showing *in vitro* dissolution of reboxetine base from different transdermal systems, according to Example 8.

Figure 9 is a diagram showing *in vitro* skin permeation of different concentrations of reboxetine base from a transdermal system, according to Example 10.

Figure 10 is a diagram showing *in vitro* dissolution of reboxetine base from reservoir patches, according to Example 12.

Figure 11 is a diagram showing *in vitro* skin permeation of 5 % reboxetine methanesulphonate solutions, according to Example 13 and Example 14.

Figure 12 is a diagram showing *in vitro* skin permeation of reboxetine methane-sulphonate from different transdermal systems according to Example 16.

Figure 13 is a diagram showing *in vitro* skin permeation of reboxetine methane-sulphonate enantiomers from different transdermal systems, according to Example 18.

5        Figure 14 is a diagram showing *in vitro* dissolution of reboxetine methanesulphonate enantiomers from different transdermal systems, according to Example 19.

#### **Detailed description of the invention**

Transdermal delivery of drugs can be achieved from topical products such as ointments or cremes or from transdermal devices. The present invention primarily re-  
10        lates to administration via transdermal devices, which usually are called transdermal patches. But other forms for topical administration, such as creams and ointments are also included.

Devices usable as transdermal patches can be categorized in many different ways. A comprehensive categorization of transdermal devices is found in Wick S. De-  
15        veloping A Drug-In-Adhesive Design for Transdermal Drug Delivery. Adhe Age 1995; 38: 18-24.

Wick essentially divides transdermal devices into the below four main groups:

- the reservoir type, in which the drug is placed in a liquid or a gel and delivered across a rate-moderating membrane to the skin;
- 20        - the matrix type, in which the drug is placed within a non-adhesive polymeric material, typically a hydrogel or soft polymer;
- the drug-in-adhesive type, in which the drug is placed within an adhesive polymer;
- the multi-laminate type, which is similar to the drug-in-adhesive design but  
25        which incorporates an additional layer of pressure sensitive adhesive to cover the entire device and affix it to the skin. A membrane can also be incorporated into this multi-laminate type as shown in Fig. 1B.

The above four main types of transdermal devices are schematically illustrated in Fig. 1A - 1D.

30        A fifth important type, not mentioned by Wick, is the iontophoretic type, which is the predominant mechanism for electrically assisted transdermal delivery. When using the iontophoretic type, an electrical potential gradient is used for transferring the drug through the skin - see further e.g. Singh P et al. Iontophoresis in Drug Delivery: Basic Principles and Applications. Crit Rev Ther Drug Carrier Syst 1994; 11: 161-213.

Besides this, electroporation, electroosmosis, electroincorporation and jet injection can be used.

Electroporation is the creation of transient aqueous pores in lipid bilayer membranes by the application of a short (msec) electric pulse (Prausnitz MR et al. Proc Int Symp Control. Rel Biact Mater 1993; 20: 95-96). By using electroporation the skin permeability will be altered such that resistance to drug transport is reduced. Electroporation has been employed in transdermal drug delivery by coupling it with iontophoresis (Bommannan D et al. Pharm Res 1994; 11: 1809-1814, Prausnitz MR et al. Proc Na Acad Sci USA 1993; 90: 10504-10508, and Riviere JE et al. J Controlled Release 1995; 36: 299-233). In these cases, a short (few milliseconds) pulse of high voltage alters the skin permeability such that subsequent iontophoresis is facilitated.

With electroosmosis the electric field creates a convective flow of water which allows hydrophilic compounds to be transported. Closely related to electroporation is electroincorporation but here particles (microspheres, liposomes) are placed on the surface of the skin and subsequent high voltage electrical pulses are employed (Riviere JE and Heit MC. Pharm Res 1997; 14: 687-697).

Jet injection can be used both for powders and liquids (Muddle AG et al. Proc Int Symp Control. Rel Biact Mater 1997; 24: 713-714, and Seyam RM et al. Urology 1997; 50: 994-998. By using jet injection a drug can be administered by a no-needle painless injection.

The above split-up into groups is not very strict as variations and combinations of each may be envisaged. So may a multi-laminate type device encompass a device with many layers in a sandwich construction, such as the drug in one layer, excipients such as enhancers in a further layer, a membrane in another layer and an adhesive in still another layer. Or it could be composed of several drug-in-adhesive layers or combinations of the above layers.

The liquid or gel used in the above reservoir type device could be hydrophilic or lipophilic, such as water, alcohols, mineral oils, silicone fluids, various copolymers, such as ethylene vinyl acetate, vinyl acetate or polyvinyl alcohol/polyvinyl pyrrolidone. The reservoir may also include dyes, inert fillers, diluents, antioxidants, antiirritants, antisensitizers, permeation enhancers, stabilizers, solubilizing agents and other pharmacologically inactive pharmaceutical agents being well known in the art.

The adhesives used are generally of three types, being the rubber type, encompassing inter alia polyisobutylenes, the acrylate type and the silicone type. The adhesiv-



es may be chemically modified, and may have a wide range of molecular weights. To the adhesive could be added several types of excipients such as fillers, stabilizers, plasticizers, buffering agents, permeation enhancers, permeation retarders, antiirritants, antisensitizers, solubilizing agents and other pharmaceutical ingredients being well known in the art.

Polymer films that may be used for making the rate-moderating membrane include, without limitation, those comprising low- and high-density polyethylene, ethyl vinyl acetate copolymers and other suitable polymers.

The backing layer serves the purposes of preventing passage of the drug and/or environmental moisture through the outer surface of the patch, and also for providing support for the system, where needed. Further the backing layer can provide occlusion, and thus increasing the rate of delivery of the drug into the skin. The backing layer may be chosen so that the end product is appealing to the users, whether children, adults, elderly people or other customer groups. The backing layer is impermeable to the passage of reboxetine or inactive ingredients being present in the formulation and can be flexible or nonflexible. Suitable materials include, without limitation, polyester, polyethylene terephthalate, some type of nylon, polypropylene, metallized polyester films, polyvinylidene chloride and aluminium foil.

The release liner can be made of the same materials as the backing layer.

As will be clear further below the invention according to the present application encompasses administration of reboxetine via all hitherto known types of devices for transdermal administration. Mainly the above categorization will be adhered to in this application. Anyhow this does not exclude that transdermal devices which might fit better according to some other categorization also are included in the present invention.

It is well known in the art that the properties of the skin as such influence the permeation of the drug through the skin into the systemic circulation. It could thus be said that the skin controls the drug permeation rate. Anyhow as the skin as such is no part of the present invention the behaviour of the skin in connection with transdermal drug delivery will not be discussed in detail. It is also well accepted in the art that when rate-controlling properties are attributed to a transdermal device is meant properties associated with the release rate from the device as such. It is also evident that when a transdermal device is designed to exhibit a certain release performance the properties of the skin need be taken into consideration during the design process.

Hydrogels (used for the matrix type and reservoir transdermal systems) are materials, which swell when placed in excess water. They are able to swell rapidly and retain large amount of water in their swollen structure. The materials do not dissolve in water and maintain three-dimensional networks. Hydrogels are usually made of hydrophilic polymer molecules that are crosslinked either by chemical bonds or other cohesion forces such as ionic interaction, hydrogen bonding or hydrophobic interaction. Hydrogels are elastic solids in the sense that there exist remembered reference configurations to which the system returns even after being deformed for a very long time (Park K et al. Biodegradable Hydrogels for Drug Delivery. Technomic Publishing Co., Inc. 1993). Examples of hydrogels are polyvinylpyrrolidone and cellulose hydrogels such as methylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, carboxymethylcellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose and microcrystalline cellulose (colloidal). Other examples are: Guar gum, gum arabic, agar, tragacanth, carrageenan, xanthan gum, algin, carbomer, dextran and chitin.

Also it could be possible to manufacture a polymer-system with no foils (backing membrane and release liner) consisting of 1, 2 or more polymers in a solvent and added drug and e.g. plasticizers and enhancers. The polymers could be a blend of hydrophilic and hydrophobic species. This product should be applied to the skin using an appropriate device where the solvent evaporates and leaving a thin invisible film. This type of systems can also be of a multilayer type where the drug could be incorporated in different layers of polymers with different release characteristics and/or alternative layers without drug that could act as a rate limiting membrane. The outer layer is most preferable hydrophobic to obtain occlusion.

The rate control ability is often a very important feature for a transdermal device in order to deliver the correct amount of drug to the patient at the correct time. Thereby maximum efficacy is achieved while side effects are minimized. Many factors influence the rate control ability of a transdermal device. In the below Table 1 the most important such factors are listed and their influence in the respective device type is marked. A plus sign indicates that the influence is strong. The absence of a plus sign does not exclude that the corresponding factor has at least some influence.

**Table 1. Type of device**

<b>Factor</b>	<b>Reservoir</b>	<b>Matrix</b>	<b>Drug-in-adhesive</b>	<b>Multilaminate</b>
Polymer type(s)	+	+	+	+
Modification of the polymer(s)		+	+	+
Activity, i.e. concentration, of drug e.g. supersaturation	+	+	+	+
Additives in polymer(s)				
- Enhancer(s)	+	+	+	+
- Cyclodextrine(s)	+	+	+	+
- Retarder(s)	+	+	+	+
pH-adjustment	+	+	+	+
Solubilizer(s)	+	+	+	+
Emulsifier(s)	+	+	+	+
Membrane(s)				
- Hydrophilic	+			
- Lipophilic	+			
- Thickness	+			
- Pore size	+			
- Density	+			
Chemical stabilizer(s)	+	+	+	+

Taking into account the convenience of wearing a patch as well as ease of manufacturing, the drug-in-adhesive and the reservoir type device are presently considered to be the best modes for carrying out the present transdermal delivery of reboxetine.

It may also be desired to include, at least in some device types, one or more transdermal permeation enhancing substance(s) in order to increase the amount of reboxetine which may permeate the skin and reach the systemic circulation, or in order to reduce the size of the patch. Enhancers suitable in the present invention may be categorized in the below groups, although enhancers not belonging to any of these groups are not excluded.

- alcohols, such as short chain alcohols, e.g. ethanol and the like, long chain fatty alcohols, e.g. lauryl alcohols, and the like, and polyalcohols, e.g. propylene glycol, glycerin and the like;

- amides, such as amides with long aliphatic chains, or aromatic amides like N,N-diethyl-m-toluamide;

- amino acids;

- azone and azone-like compounds;

5       - essential oils, i.e. essential oils or constituents thereof, such as l-carvone, l-menthone-menthol, and the like;

- fatty acids and fatty acid esters, such as oleic acid, lauric acid and the like, further esters of fatty acids, such as isopropyl myristate, and various esters of lauric acid and of oleic acid and the like;

10       - macrocyclic compounds, such as cyclopentadecanone and cyclodextrins;

- phospholipid and phosphate compounds, such as phospholipids;

- 2-pyrrolidone compounds; and

- miscellaneous compounds, like sulfoxides, such as dimethyl sulfoxides, and fatty acid ethers, such as Laureth-9 and polyoxylaurylether.

15       Combinations of enhancers from different groups in the above categorization may prove very useful and efficient.

For overview of enhancers, see further e.g. Santus GC et al. Transdermal enhancer patent literature. J Control Release 1993; 25: 1-20, and Smith EW et al. Percutaneous penetration enhancers. CRC Press Inc. 1995.

20       Detailed description of the invention.

The following examples are intended to illustrate, but not to limit the scope of the invention, although the embodiments named are of particular interest for our intended purposes.

Apparatus used in the examples

25       As disclosed below.

Materials

As disclosed below.

Drug

30       Reboxetine methanesulphonate was supplied by Pharmacia & Upjohn (Kalamazoo, USA).

Polymers

Eudragit E 100 aqueous and organic based were supplied by Röhm GmbH Chemische Fabrik, Polyethylene glycol 400 (PEG 400) was supplied by Merck-Schuchardt, Polyvidone 90 (PVP 90) was supplied by BASF, MA-24 was from Adhesive

Research Inc., Durotak 387-2287, 387-2516 and 387-2852 were supplied by National Starch & Chemical.

#### Foils

Drug-in-adhesive patch: The siliconized polyester release liner (FL2000-75 PET 1S) was obtained from Rexam Release and the pigmented occlusive backing membrane (Scotchpak 1109) was obtained from 3M Corp.

Reservoir patch: 3M backing membrane (Scotchpak 9732), 3M release liner (Scotchpak 9733), plus the rate controlling membranes; CoTran membranes (with 9 %, 19 % and 28 % vinyl acetate (VA)) were all from 3M Corp.

#### Other materials

Azone was obtained from Discovery Therapeutics Inc., Methyllaurat was supplied by Fluka.

Other chemicals used were of analytical grade.

#### Patch formulation studies

Patch formulations were prepared by adding reboxetine base to each of the chosen polymers (acrylates, polyisobutylenes, PVP/PEG). The drug gels were coated onto a siliconized polyester release liner (FL2000-75 PET 1S) by using a coating equipment (Lab Drawdown Coater, Type LC-100) The laminates were dried and having a dry coat weight of approximately 100 g/m<sup>2</sup>. A backing membrane (Scotchpak 1109) was laminated onto the dried drug gel, resulting in a drug-in-adhesive laminate. Patches were die-cut from the finished sheet, pouch-packed in Barex foil and stored at room temperature until use. Any deviation from the above will be mentioned under the individual examples.

#### Reservoir patch formulation study

5 % reboxetine base was dissolved in ethanol and 5 % reboxetine methanesulphonate was dissolved in water. The solutions were thereafter filled in reservoir patches by use of a reservoir patch machine (A&D, GmbH, Type PF-80). As backing membrane Scotchpak 9732 was used and as release liner Scotchpak 9733 was used. The rate controlling membranes consisted either of CoTran 9702 (9 % vinyl acetate) or CoTran 9728 (19 % vinyl acetate).

#### Quantitative HPLC-determination of reboxetine content

The content of reboxetine was determined using a HPLC method. The system consisted of a HP 1100 pump or the equivalent, a HP1100 autosampler or the equivalent with a 20 µl loop, a HP1100 detector or the equivalent and a HP Chemstation integrator

or the equivalent. The column was Nuclosil 5C8, 150 x 4,6 mm and the mobile phase was a mixture of 0,1 M phosphate buffer pH 3,0 – acetonitrile (70+30). The flow was 1,0 ml/min and the detection wavelength was 280 nm.

#### In vitro dissolution studies

- 5        *In vitro* dissolution studies were performed by using a modified USP Type 5 paddle apparatus. The apparatus was modified by the use of a convex screen to hold the transdermal system in position during testing. The system consisted of a Pharma Test Type PTW SIIC six-vessel dissolution apparatus connected to a Pharma Test Type PTFCH Fraction collector or equivalent. As dissolution medium was used 0,05 M phosphate buffer, pH 7,4 equilibrated to 32°C. Samples were withdrawn at certain time intervals, and the amount of reboxetine was determined by HPLC. Amount of drug permeated per cm<sup>2</sup> was plotted as a function of time.

#### In vitro skin permeation studies

- 15        *In vitro* skin permeation results were obtained from studies on pig or human skin using Franz diffusion cells. Using a dermatome (Zimmer Electric Dermatome 8821, Zimmer Chirurgie) isolated 765 µm skin.

- 20        The skin was mounted in the diffusion cells with an available diffusion area of 1,8 cm<sup>2</sup>. The inner side of the epithelium was exposed to 12,1 ml receptor phase (0,05 M phosphate buffer, pH 7,4) at 37±1°C, corresponding to 32°C on the donor side of the skin. Samples were withdrawn periodically from the receptor phase up to 48 hours and immediately replaced by fresh receptor phase. The cumulated amount of reboxetine in the receptor phase divided by skin area was plotted as a function of time. Fluxes (µg/cm<sup>2</sup>/h) were obtained by linear regression of data at steady state. The quantitative determination of reboxetine was performed using a HPLC method. Pigskin was
- 25        applied for all *in vitro* skin permeation studies except for Example 7.

#### Examples

##### Example 1

*In vitro* skin permeation studies from saturated solutions of reboxetine base.

##### Solution 1

- 30        Reboxetine base was dissolved in water equal to 6,6 mg/ml.

##### Solution 2

Reboxetine base was dissolved in propylene glycol equal to 280 mg/ml.

##### Solution 3

Reboxetine base was dissolved in ethanol equal to 344 mg/ml.

Solution 4

Reboxetine base was dissolved in isopropylmyristate equal to 119 mg/ml.

*In vitro* skin permeation of reboxetine base from solution 1 to 4 through dermatomed pig skin, 765  $\mu\text{m}$  was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 2. An increase in the amount of reboxetine base permeated is seen in the following order: isopropylmyristate > ethanol > propylene glycol > water. The results show that it is possible to adjust the flux through the skin by changing the solvent. It is further obvious that varying the concentration of reboxetine in accordance with Ficks first law can alter the flux.

Example 2

*In vitro* skin permeation studies of 5 % reboxetine base solutions.

Solution 5

5 % reboxetine base dissolved in ethanol.

Solution 6

5 % reboxetine base dissolved in propylene glycol.

*In vitro* skin permeation of reboxetine base from solution 5 and 6, respectively through dermatomed pig skin, 765  $\mu\text{m}$ , was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 3. An increase in the amount of reboxetine base permeated is seen in the following order: ethanol > propylene glycol. The results show that it is possible to adjust the flux through the skin by changing the solvent.

Example 3

*In vitro* permeation studies from solutions of 5 % reboxetine base added enhancers.

Solution 7

5 % reboxetine base dissolved in ethanol, added 5 % Azone.

Solution 8

5 % reboxetine base dissolved in ethanol, added 5 % Methyllaurat.

*In vitro* skin permeation of reboxetine base from solution 7 and 8, respectively, through dermatomed pigskin, 765  $\mu\text{m}$ , was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 3. An increase in the amount of reboxetine base permeated is seen in the following

order: Methyllaurat > Azone. The results show a significant increase in flux of reboxetine base when enhancer is added the solutions.

**Example 4**

5 *In vitro* skin permeation studies across synthetic membranes and dermatomed pigskin, 765  $\mu\text{m}$ , from 5 % reboxetine base solutions, simulating the reservoir type transdermal device.

**Solution 9**

5 % reboxetine base dissolved in ethanol.

**Solution 10**

10 5 % reboxetine base dissolved in propylene glycol.

*In vitro* skin permeation of reboxetine base from solution 9 and 10, respectively, across 3 different synthetic membranes was investigated using Franz diffusion cells.

Membranes of the following types were used: CoTran 9702 (microporous polyethylene film) with 9 % vinylacetate (VA), CoTran 9728 with 19 % vinylacetate and an  
15 experimental CoTran membrane with 28 % vinylacetate. The three mentioned CoTran membranes were applied to solution 9, whereas only CoTran (19 % VA) and CoTran (28 % VA) were applied to solution 10. The membranes were placed on top of dermatomed pigskin. *In vitro* skin permeation of reboxetine base from solution 9 and 10, through dermatomed pig skin, 765  $\mu\text{m}$ , was investigated using Franz diffusion cells.  
20 The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 4. The membranes impede the flux of reboxetine base considerably; increased flux is observed with increased amount of VA in the membranes. The results show that it is possible to control the permeation rate of reboxetine base from a reservoir type device by changing the membrane.

25 **Example 5**

**System 1 (drug-in-adhesive, acrylate)**

**Loading of different Durotak acrylates with reboxetine base.**

Patches containing approximately 1 mg/cm<sup>2</sup> reboxetine base in Durotak 387-2287, 387-2516 and 387-2852 were manufactured according to the "patch formulation  
30 studies" described previously. The drug gels were coated and dried at 80°C for 10 min., resulting in a dry coat weight of approximately 100 g/m<sup>2</sup>.



System 2 (drug-in-adhesive, hydrophilic matrix)Loading of hydrophilic matrix with reboxetine base

A patch containing approximately 1 mg/cm<sup>2</sup> reboxetine base in a mixture of polyvidone 90 : polyethylene glycol 400 (1:1) was manufactured. Reboxetine base, polyvidone 90 and polyethylene glycol 400 were dissolved in ethanol 99,9 %. The drug gel was coated and dried at 50°C for 4 hours, resulting in a dry coat weight of approximately 100 g/m<sup>2</sup>.

System 3 (drug-in-adhesive, polyisobutylene)Loading of polyisobutylene with reboxetine base

A patch containing approximately 1 mg/cm<sup>2</sup> reboxetine base in MA-24 was manufactured. The drug gel was coated and dried at 80°C for 10 min, resulting in a dry coat weight of approximately 100 g/m<sup>2</sup>.

System 4 (drug-in-adhesive, methacrylate).Loading of Eudragit methacrylate with reboxetine base.

A patch containing approximately 1,05 mg/cm<sup>2</sup> reboxetine base in Eudragit E 100, organic based. 2,9 g of reboxetine base was added to 40 g of Eudragit E 100, organic based. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coat weight of approximately 100 g/m<sup>2</sup>.

Example 6

*In vitro* skin permeation studies of the transdermal drug delivery System 1, 2, 3 and 4 according to Example 5 (Fig. 5).

*In vitro* skin permeation of reboxetine base through dermatomed pig skin, 765 µm was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 5. Fluxes are in the range of 0 – 15,8 µg/cm<sup>2</sup>/h. It appears that different fluxes can be obtained by applying different polymers.

Example 7

*In vitro* skin permeation studies applying human skin.

*In vitro* skin permeation studies of the transdermal drug delivery System 1 (Durotak 387-2287) and 2 (polyvidone90:polyethylene glycol400) according to Example 5 (Fig. 6).

*In vitro* skin permeation of reboxetine base through dermatomed human skin, 765 µm was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig.6. Fluxes are in the

range of 7,1 – 18,9  $\mu\text{g}/\text{cm}^2/\text{h}$ . Higher fluxes is obtained when applying human skin compared to applying pig skin.

### Example 8

Stability studies were carried out on the transdermal drug delivery Systems 1  
5 (Durotak 387-2287 and Durotak 387-2852) according to Example 5. The patches were stored at 25°C/60 % R.H. and 40°C/75 % R.H.

Quantitative determination of reboxetine base was done by HPLC after 0, 1, 2  
and 3 months of storage. (Table 2). Likewise was *in vitro* dissolution studies performed at 0, 1, 2 and 3 months of storage (Fig. 7 and 8). From Table 2 it appears that the quan-  
10 titative amount of reboxetine base after storage is consistent with the initial value, and no degradation has occurred. When comparing the release profiles in Fig. 7 and 8 it is apparent that no change in release has occurred after storage. Furthermore it is seen that using different polymers can alter the release profile.

Below Table 2 shows quantitative determination of reboxetine base after 0, 1, 2  
15 and 3 months of storage, according to Example 8.

**Table 2 Stability of reboxetine base in different Durotak polymers**

Concentration 1  $\text{mg}/\text{cm}^2$

Coat weight 100  $\text{g}/\text{m}^2$

Storage time	Temp. 25°C 60 % R.H.		Temp. 40°C 75 % R.H.	
	Durotak 2852 Reboxetine base ( $\text{mg}/\text{cm}^2$ )	Durotak 2287 Reboxetine base ( $\text{mg}/\text{cm}^2$ )	Durotak 2852 Reboxetine base ( $\text{mg}/\text{cm}^2$ )	Durotak 2287 Reboxetine base ( $\text{mg}/\text{cm}^2$ )
Zero	0,72	0,83	0,72	0,83
1 month	0,75	0,84	0,76	0,78
2 months	0,76	0,78	0,67	0,72
3 months	0,79	0,79	0,78	0,72

20

### Example 9

System 5 (drug-in-adhesive, acrylate)

Loading of acrylate with reboxetine base in different concentrations (same dry coat weight).

Patches containing approximately 0,7  $\text{mg}/\text{cm}^2$ , 1,05  $\text{mg}/\text{cm}^2$  and 1,4  $\text{mg}/\text{cm}^2$  re-  
25 boxetine base in Durotak 387-2287 were manufactured according to the "patch formu-

lation studies" described previously. The drug gels were coated and dried at 80°C for 10 min, resulting in a dry coat weight of approximately 140 g/m<sup>2</sup>.

#### Example 10

5        *In vitro* skin permeation studies of the transdermal drug delivery System 5, according to Example 9 (Fig. 9).

*In vitro* skin permeation of reboxetine base through dermatomed pig skin, 765 µm was investigated using Franz diffusion cells. The cumulative amount of reboxetine base in the receptor solution versus time is shown in Fig. 9. Fluxes are in the  
10      range of 1,6 – 2,9 µg/cm<sup>2</sup>/h. It is seen that the highest flux is obtained from the patch having the highest drug load of reboxetine base. However, no clear correlation between the medium and minimum drug load, and permeated amount of reboxetine base is evident from Fig. 9.

#### Example 11

15        System 6 (reservoir patch)

      5 % reboxetine base dissolved in ethanol. 750µl were filled in each reservoir patch using the reservoir machine. As backing membrane Scotchpak 9732 was used and as release liner Scotchpak 9733 was used. Two different rate controlling membranes were used, CoTran 9702 with 9 % vinyl acetate and CoTran 9728 with 19 % vinyl acetate.  
20      No adhesive was applied to the reservoir patch.

#### Example 12

*In vitro* dissolution studies of the transdermal drug delivery System 6, according to Example 11 (Fig. 10).

      Reservoir patches of 20,4 cm<sup>2</sup> were applied to the disk assembly, using a suitable adhesive with the release surface facing up. Samples were withdrawn periodically  
25      up to 24 hours. The amount of reboxetine base released from the patches was expressed in mg reboxetine base per cm<sup>2</sup>. The results show that only a relatively small amount of reboxetine base is released from the reservoir patches. A decreased release is observed with decreased amount of VA in the CoTran membranes. The results show that it is  
30      possible to control the release rate of reboxetine base from a reservoir type device by changing the CoTran membrane or any other membranes applied.

#### Example 13

*In vitro* skin permeation studies of 5 % reboxetine methanesulphonate solutions

Solution 11

5 % reboxetine methanesulphonate dissolved in water.

Solution 12

5 % reboxetine methanesulphonate dissolved in propylene glycol.

- 5        *In vitro* skin permeation of reboxetine methanesulphonate from solution 11 and 12, respectively, through dermatomed pigskin, 765  $\mu\text{m}$ , was investigated using Franz diffusion cells. The cumulative amount of reboxetine methanesulphonate in the receptor solution versus time is shown in Fig. 11. An increase in the amount of reboxetine methanesulphonate permeated is seen in the following order: water > propylene glycol.
- 10      The results show that it is possible to adjust the flux through the skin by changing the solvent. The results also show that surprisingly it is possible to use reboxetine methanesulphonate and still obtain useful fluxes.

Example 14

- 15        *In vitro* permeation studies from solutions of 5 % reboxetine methanesulphonate added enhancers.

Solution 13

5 % reboxetine methanesulphonate dissolved in water, added 5 % Azone.

Solution 14

- 20        5 % reboxetine methanesulphonate dissolved in propylene glycol, added 5 % Methyllaurat.

- In vitro* skin permeation of reboxetine methanesulphonate from solution 13 and 14, respectively, through dermatomed pigskin, 765  $\mu\text{m}$ , was investigated using Franz diffusion cells. The cumulative amount of reboxetine methanesulphonate in the receptor solution versus time is shown in Fig. 11. An increase in the amount of reboxetine methanesulphonate permeated is seen in the following order: Azone > Methyllaurate.
- 25        The results show a significant increase in flux of reboxetine methanesulphonate when enhancer is added to the solutions.

Example 15System 7 (drug-in-adhesive, acrylate)

- 30        Loading of Durotak acrylate with reboxetine methanesulphonate

A patch containing approximately 1  $\text{mg}/\text{cm}^2$  reboxetine methanesulphonate in Durotak 387-2287 was manufactured according to the "patch formulation studies" described previously. The drug gels were coated and dried at 80°C for 10 min., resulting in a dry coat weight of approximately 100  $\text{g}/\text{m}^2$ .

System 8 (drug-in-adhesive, hydrophilic matrix)Loading of hydrophilic matrix with reboxetine methanesulphonate

A patch containing approximately 1 mg/cm<sup>2</sup> reboxetine methanesulphonate in a mixture of polyvidone 90 : polyethylene glycol 400 (1:1) was manufactured. Reboxetine methanesulphonate, polyvidone 90 and polyethylene glycol 400 were dissolved in ethanol 99,9 %. The drug gel was coated and dried at 50°C for 4 hours, resulting in a dry coat weight of approximately 100 g/m<sup>2</sup>.

System 9 (drug-in-adhesive, methacrylate)Loading of Eudragit methacrylate with reboxetine methanesulphonate.

A patch containing approximately 1 mg/cm<sup>2</sup> reboxetine methanesulphonate in Eudragit E 100, aqueous based, was manufactured. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coatweight of approximately 100 g/m<sup>2</sup>.

Example 16

*In vitro* skin permeation studies of the transdermal drug delivery System 7, 8 and 9 according to Example 15 (Fig. 12).

*In vitro* skin permeation of reboxetine methanesulphonate through dermatomed pig skin, 765 µm was investigated using Franz diffusion cells. The cumulative amount of reboxetine methanesulphonate in the receptor solution versus time is shown in Fig. 12. Fluxes are in the range of 0,9 – 6,6 µg/cm<sup>2</sup>/h. It appears that different fluxes can be obtained by applying different polymers.

Example 17System 10 (drug-in-adhesive, methacrylate)Loading of Eudragit methacrylate with reboxetine methanesulphonate enantiomers

A: Patch containing approximately 0,75 mg/cm<sup>2</sup> (racemic) reboxetine methanesulphonate in Eudragit E 100, aqueous based. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coat weight of approximately 75 g/m<sup>2</sup>.

B: Patch containing approximately 0,75 mg/cm<sup>2</sup> (S,S (+)enantiomer) reboxetine methanesulphonate in Eudragit E 100, aqueous based. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coat weight of approximately 75 g/m<sup>2</sup>.

C: Patch containing approximately 0,75 mg/cm<sup>2</sup> (R,R (-)enantiomer) reboxetine methanesulphonate in Eudragit E 100, aqueous based. The drug gel was coated and dried at 60°C for 10 min, resulting in a dry coat weight of approximately 75 g/m<sup>2</sup>.

**Example 18**

*In vitro* skin permeation studies of the transdermal drug delivery System 10 (A, B and C) according to Example 17 (Fig. 13).

*In vitro* skin permeation of enantiomers of reboxetine methanesulphonate through dermatomed pig skin, 765  $\mu\text{m}$  was investigated using Franz diffusion cells. The cumulative amount of reboxetine methanesulphonate enantiomers in the receptor solution versus time is shown in Fig. 13. Fluxes are in the range of 5,3 – 7,4  $\mu\text{g}/\text{cm}^2/\text{h}$ . The enantiomers show no noticeable difference in skin permeation rate, which means that the individual enantiomers can be used in the transdermal formulations

**Example 19**

*In vitro* dissolution of the transdermal drug delivery System 10 (A, B, and C) according to Example 17 (Fig. 14).

Patches of 10  $\text{cm}^2$  were applied to the disk assembly, using a suitable adhesive with the release surface facing up. Samples were withdrawn periodically up to 24 hours. The amount of reboxetine methanesulphonate enantiomers released from the patches was expressed in mg reboxetine methanesulphonate per  $\text{cm}^2$ . From Fig. 14 no difference in release profiles from the different enantiomers is observed.

**Example 20**

Primary skin irritation study in rabbit and test for delayed contact hypersensitivity using the Buehler test (performed by Scantox, Denmark).

The primary skin irritating effect of reboxetine methanesulphonate was investigated according to the method in the OECD Guideline No. 404, "Acute Dermal Irritation/Corrosion", 1992 and EEC Guideline B.4 "Acute Toxicity (skin irritation)", 29.12.1992.

0,5 g of reboxetine methanesulphonate moistened with approximately 0,3 ml 0,9 % NaCl was applied on 3 rabbits. After 4 hours of exposure reboxetine methanesulphonate was removed and the skin was examined 1, 24, 48 and 72 hours after termination of exposure. For reboxetine methanesulphonate the mean score for both erythema and oedema was 0.0. According to this reboxetine methanesulphonate was not classified as skin irritating.

The dermal sensitising potential of reboxetine methanesulphonate was investigated according to one of the methods recommended in the OECD Guideline NO. 406, "Skin Sensitisation, Description of the Buehler test method", 1992 and the EEC Direc-

tive published in: "Official Journal of the European Communities" No: L 383A, volume 35, 29.12.1992, part B6: Skin Sensitisation, the Buehler test.

0,1 g reboxetine methanesulphonate moistened with 0,3 ml 0,9 % NaCl was selected for the dermal inductions and for the challenge. It was concluded that no evidence of delayed contact hypersensitivity was seen after treatment with reboxetine methanesulphonate.

A iontophoretic type device may be manufactured essentially according to embodiments disclosed in e.g. Parminder Singh et al, "Iontophoresis in Drug Delivery: Basic Principles and Applications", Critical Reviews in Therapeutic Drug Carrier Systems, 1994; 11 (2&3):161-213. The administration of reboxetine or derivatives thereof is not disclosed in this reference. Anyhow it lies within the present invention to modify, using the disclosure in the present application, the embodiments according to said reference to become suitable for the administration of reboxetine.

The above examples show that it is possible to administer reboxetine and to control its release rate using all known types of devices for transdermal drug administration.

Various carriers and vehicles for reboxetine may be used in the transdermal administration. One such carrier is cyclodextrine, especially  $\beta$ -cyclodextrine. Reboxetine can be bound in the cavities of cyclodextrines to form so called inclusion complexes. Binding reboxetine to a cyclodextrine leads either to increased delivery rate or to decreased delivery rate depending on the reboxetine-cyclodextrine ratio.

#### Dosage

In the Investigator's Brochure on reboxetine is stated that for dose-response, selection of reboxetine dose regimens for oral intake was accomplished in an early phase II, non-randomized, dose-finding study, which was adequate for finding the daily dose associated with intolerance (12 mg/day) and the daily doses associated with minimal side-effect and maximal response rate 8 and 10 mg/day), although in view of the non-randomized conditions no conclusions about dose-response could be drawn.

From the above findings it is relevant to conclude that a useful dosage of transdermally administered reboxetine according to the present invention for the conditions stated above would preferably range from 0.1 mg/day to 20 mg/day. Thereby is not excluded that also lower and higher daily dosages would be useful. The exact amounts should be determined in accordance with acknowledged principles, taking into account age, weight, condition to be treated and other relevant parameters.

The data of Fig. 13 show that an apparent 0-order delivery of reboxetine through the skin takes place from about 5 to 48 hours. This 0-order delivery may continue for at least up to a week. Such a once-weekly patch will greatly improve patient compliance, which is important for patients, which often use tolterodine.

5        It should therefore also be contemplated that a device for transdermal delivery during 2 or more days would further facilitate the use of the transdermal formulation. It is possible to design a device delivers reboxetine for a predefined period of time, preferably 12, 24 or 48 hours, or even up to 7 or 14 days.

         It might be desirable to use higher dosages of reboxetine during the day or night.  
10       It is within the present invention to administer reboxetine in such a way that a therapeutically effective systemic level of reboxetine prevails to a higher extent during the day or the night. The above object is achievable by applying the transdermal device at the appropriate time during day or night in combination with designing the device with the appropriate release profile. The same rules for a device designed to deliver reboxetine to  
15       a lower extent during the day or the night.

         When reboxetine is administered in a transdermal device the latter should preferably be occlusive, which means that the device does not permit water to migrate outwardly from the skin area covered by the device or at least with a lower rate than the rate of the skins ordinary transepidermal water loss. Thereby the hydration of the skin is  
20       increased which favors the penetration of reboxetine through the skin.

         For convenience and/or in order to achieve a more rapid increase in plasma level it is possible to design a set of formulations of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, which comprises at least one device for transdermal delivery and at least one formulation for oral, sublingual, buccal, nasal, pulmonary, rectal and/or other transmucosal administration.  
25       In all the different embodiments of the present invention reboxetine may be present in just one of its above-presented forms or as a mixture of two or more forms.



## CLAIMS

1. Device for transdermal administration, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof,  
5 and optionally together with pharmaceutically acceptable carrier(s), to a human being or an animal.

2. Device for transdermal administration, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), to a human being or  
10 an animal and that it is devoid of a matrix comprising lecithin gel.

3. Device for transdermal administration according to claim 1 or 2, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), to a human being or an animal in order to achieve an antidepressant effect for  
15 treating depression or symptoms associated with this condition.

4. Device for transdermal administration according to claim 1 or 2, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), to a human being or an animal in order to achieve an effect for treating addictive  
20 disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders,  
25 obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, or symptoms associated with said conditions.  
30

5. Device for transdermal administration according to claim 1 or 2, characterized in that it administers reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable car-

rier(s), to a human being or an animal in order to achieve an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect.

6. Device for transdermal administration according to anyone of claims 1 - 5, characterized in that reboxetine essentially is in its R-isomeric form.

5 7. Device for transdermal administration according to anyone of claims 1 - 5, characterized in that reboxetine essentially is in its S-isomeric form.

8. Device for transdermal administration according to anyone of claims 1 - 5, characterized in that reboxetine essentially is in racemic form.

9. Device for transdermal administration according to anyone of claims 1 - 8,  
10 characterized in that it is of the reservoir type, the matrix type, the drug-in-adhesive type, the multi-laminate type, the polymer-system with no foils type, and/or the iontophoretic type or combinations thereof, preferably of the drug-in-adhesive type or the reservoir type or combinations of these two types.

10. Device for transdermal administration according to anyone of claims 1 - 8,  
15 characterized in that it is of the electroporation, electroosmosis, electroincorporation or jet injection type.

11. Device for transdermal administration according to anyone of the preceding claims, characterized in that it has a loading of reboxetine providing for a daily dosage of from about 0.1 mg to about 20 mg.

20 12. Device for transdermal administration according to anyone of the preceding claims, characterized in that it delivers reboxetine for a predefined period of time, preferably 12, 24 or 48 hours, or up to 7 or 14 days.

13. Device according to anyone of the preceding claims, characterized in that reboxetine is present in a complex with cyclodextrin, preferably  $\beta$ -cyclodextrin.

25 14. Device according to anyone of the preceding claims, characterized in that it has a release profile being such that it, when applied on the skin at the appropriate time during day or night, administers reboxetine in such a way that a therapeutically effective systemic level of reboxetine prevails mainly during such periods of time during day and night when an antidepressant effect is most desirable.

30 15. Device according to anyone of the preceding claims, characterized in that it further comprises a substance enhancing transdermal penetration.

16. Device according to anyone of the preceding claims, characterized in that it further comprises a substance reducing irritant reactions.

17. Device according to anyone of the preceding claims, c h a r a c t e r i z e d in that it is occlusive.

18. Set of formulations of reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s), c h a r a c t e r i z e d in that it comprises at least one device according to any-  
5 one of the preceding claims and at least one formulation for oral, sublingual, buccal, nasal, pulmonary, rectal and/or other transmucosal administration.

19. Use of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically accept-  
10 able carrier(s), for the manufacture of a composition to be administered transdermally for achieving an antidepressant effect and/or an effect against symptoms associated with this condition.

20. Use of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically accept-  
15 able carrier(s), for the manufacture of a composition to be administered transdermally for treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclo-  
20 thymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal  
25 affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome or symptoms associated with said conditions.

21. Use of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically accept-  
30 able carrier(s), for the manufacture of a composition to be administered transdermally for achieving an anti-reserpine effect and/or a noradrenaline reuptake inhibiting effect.

22. Use according to anyone of claims 19 - 21, c h a r a c t e r i z e d in that reboxetine essentially is in its R-isomeric form.

23. Use according to anyone of claims 19 - 21, characterized in that reboxetine essentially is in its S-isomeric form.

24. Use according to anyone of claims 19 - 21, characterized in that reboxetine essentially is in racemic form.

5        25. Use according to anyone of claims 19 - 24, characterized in that the transdermal delivery is carried out using a device for transdermal delivery, such device especially being of the reservoir type, the matrix type, the drug-in-adhesive type, the multi-laminate type, the polymer-system with no foils type, and/or the iontophoretic type or combinations thereof, preferably of the drug-in-adhesive type or the reservoir  
10        type or combinations of these two types.

26. Use according to anyone of claims 19 -24, characterized in that the transdermal delivery is carried out using a device of the electroporation, electroosmosis, electroincorporation or jet injection type.

15        27. Use according to claim 25 or 26, characterized in that more than one transdermal device is used at a time.

28. Method for achieving an antidepressant effect in a living body or for achieving an effect when treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit  
20        hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral  
25        neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, or for achieving an anti-reserpine and/or noradrenaline reuptake inhibiting effect, by transdermal administration of a compound comprising reboxetine, optionally  
30        encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s).

29. Method according to claim 28, characterized in that reboxetine essentially is in its R-isomeric form.

30. Method according to claim 28, characterized in that reboxetine essentially is in its S-isomeric form.

31. Method according to claim 28, characterized in that reboxetine essentially is in racemic form.

5 32. Method according to anyone of claims 28 -31 wherein the treatment is achieved through systemic effect of the transdermally administered compound.

33. Method according to anyone of claims 28- 32 wherein the transdermal administration is carried out using a device for transdermal delivery, such device especially being of the reservoir type, the matrix type, the drug-in-adhesive type, the multi-laminate type, the polymer-system with no foils type, and/or the iontophoretic type or combinations thereof, preferably of the drug-in-adhesive type or the reservoir type or combinations of these two types.

34. Method according to anyone of claims 28- 32 wherein the transdermal administration is carried out using a device for transdermal delivery device of the electroporation, electroosmosis, electroincorporation or jet injection type.

35. Method according to anyone of claims 28 - 34 wherein more than one device for transdermal delivery is used at a time.

36. Method for achieving an antidepressant effect and/or symptoms associated with this condition in a living body or for achieving an effect when treating addictive disorders and withdrawal syndromes, adjustment disorders, age-associated learning and mental disorders, anorexia nervosa, apathy, attention-deficit disorders due to general medical conditions, attention-deficit hyperactivity disorders, bipolar disorders, bulimia nervosa, chronic fatigue syndrome, conduct disorders, cyclothymic disorders, depression, dysthymic disorders, fibromyalgia and other somatoform disorders, stress incontinence, generalized anxiety disorders, inhalation disorders, an intoxication disorders, obesity, obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorders, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder, psychotic disorders, seasonal affective disorder, sleep disorder, social phobia, specific developmental disorders and selective serotonin reuptake inhibition (SSRI) "poop out" syndrome, or for achieving an anti-reserpine and/or noradrenaline reuptake inhibiting effect, by transdermal administration of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s) in combination with oral, sublingual, buccal, nasal, pulmonary, rectal and/or other transmucosal administration.

tion of a compound comprising reboxetine, optionally encompassing salts, prodrugs and metabolites thereof, and optionally together with pharmaceutically acceptable carrier(s).

37. Method according to anyone of the claims 28 - 36, characterized in that reboxetine is administered in such a way that a therapeutically effective systemic level of reboxetine prevails mainly during those periods of time during day and night when an effect is most desirable.

38. Method according to anyone of the claims 28 - 36, characterized in that reboxetine is administered in such a way that a less than therapeutically effective systemic level of reboxetine prevails mainly during those periods of time during day and night when an antidepressant effect is less desirable.

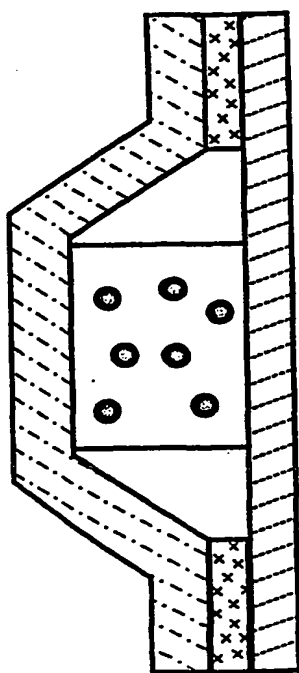


Fig. 1 A Matrix

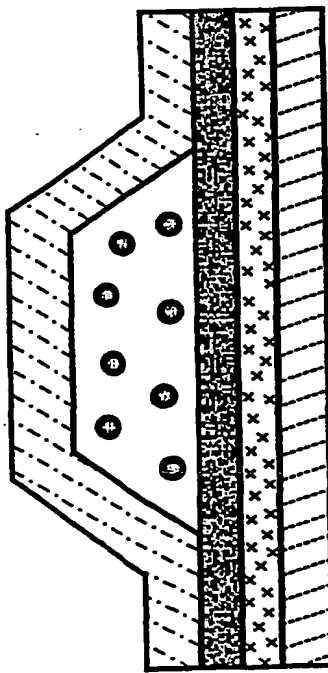


Fig. 1 C Reservoir

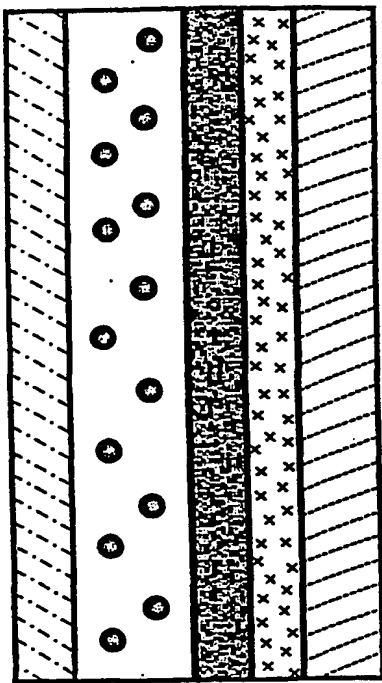


Fig. 1 B Multi-laminate

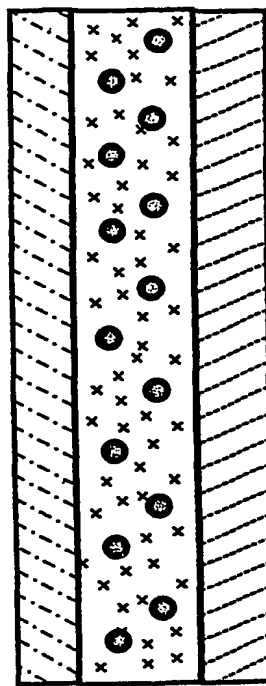
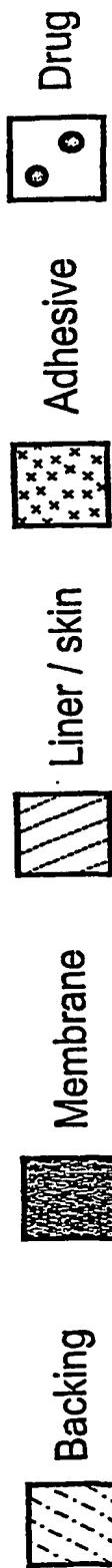


Fig. 1 D Drug-in-adhesive



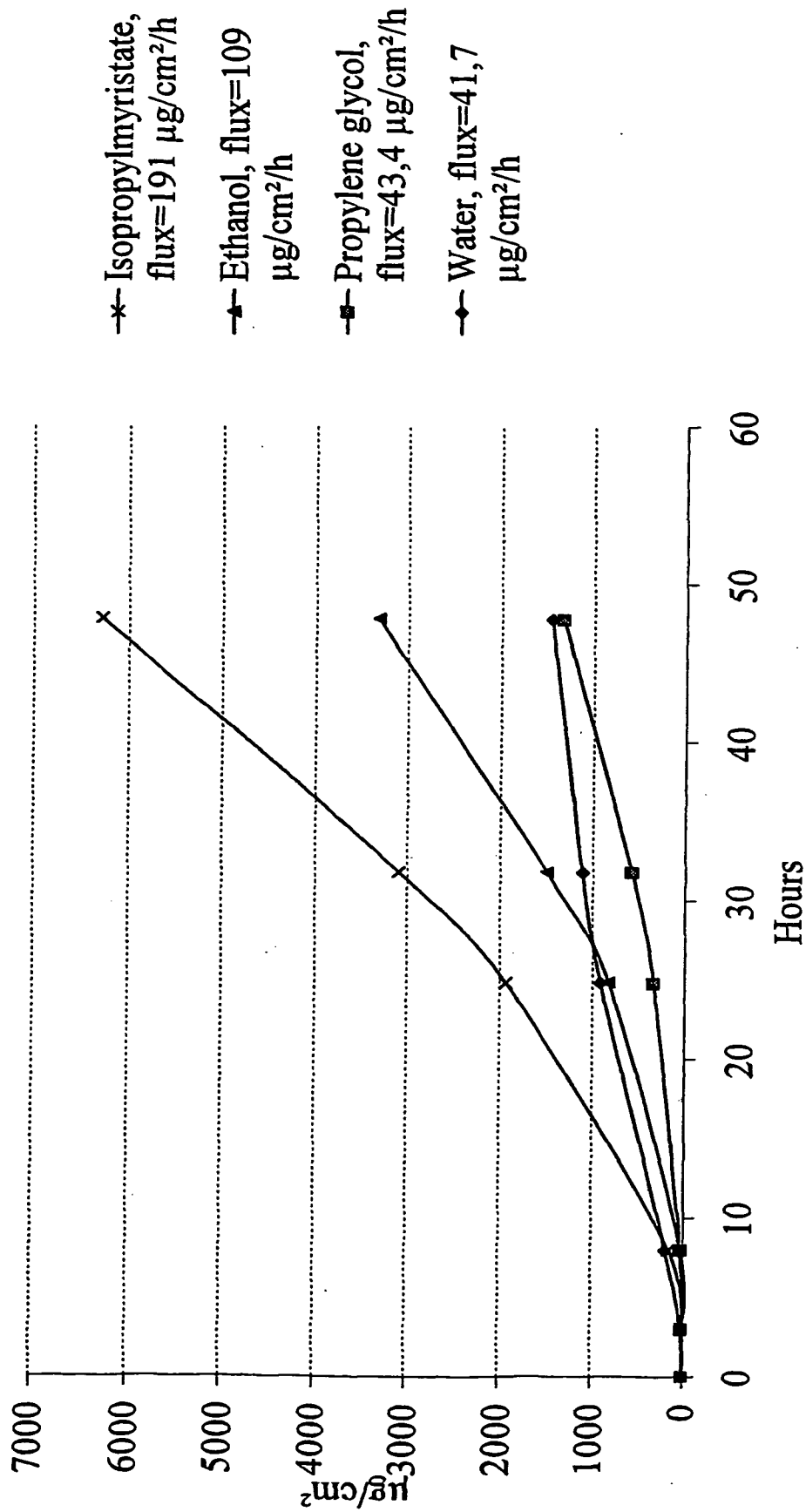


Figure 2



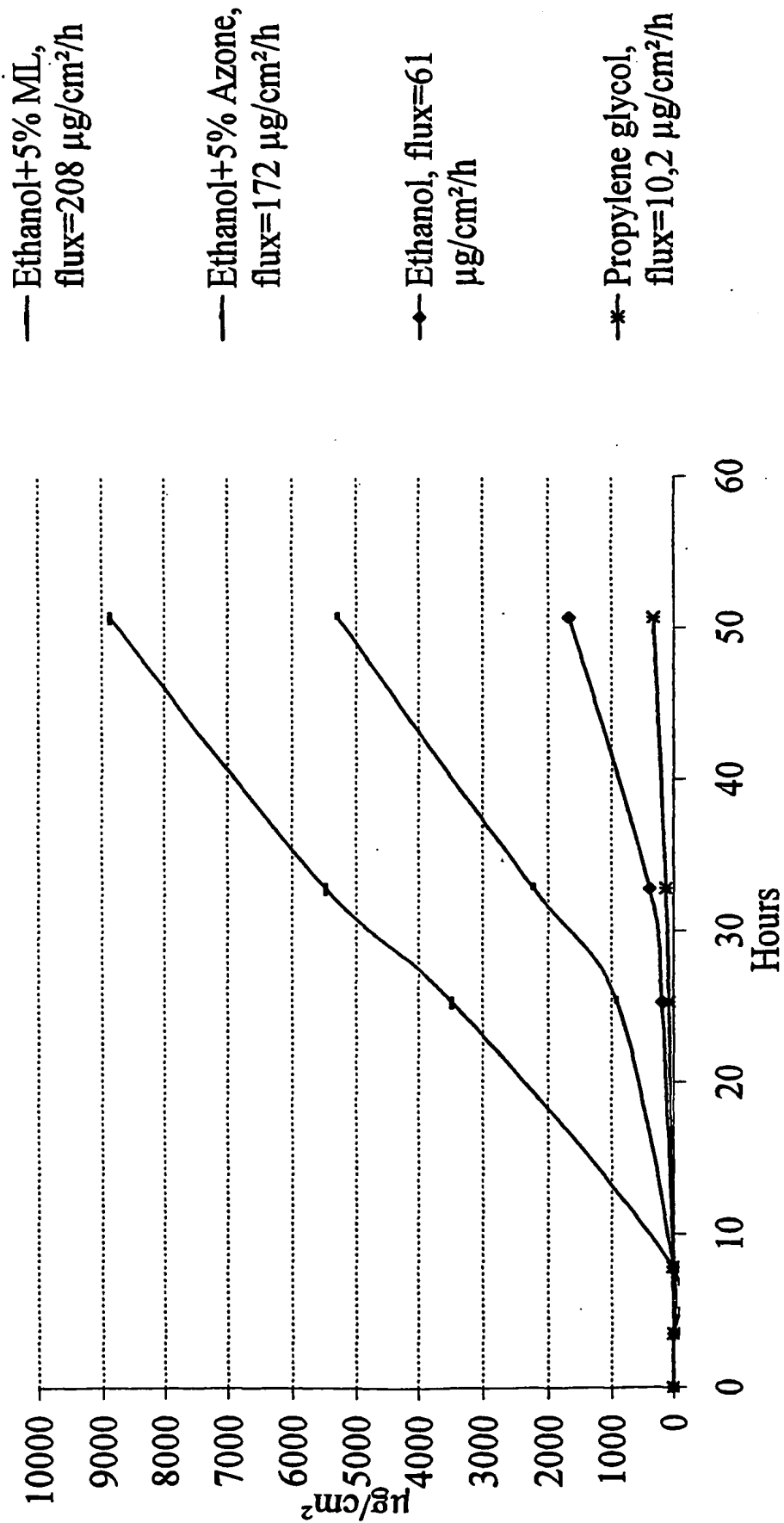


Figure 3

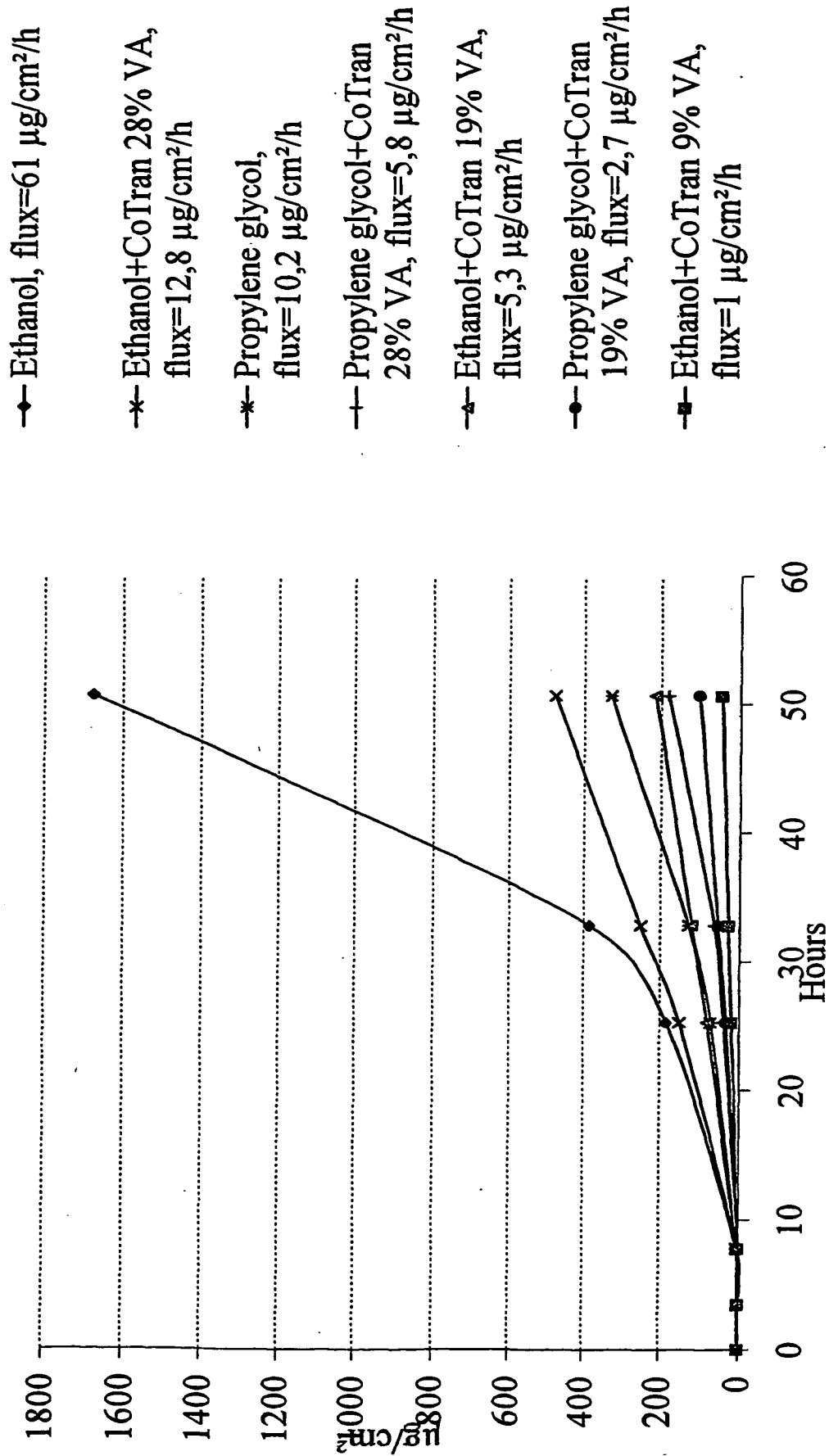


Figure 4

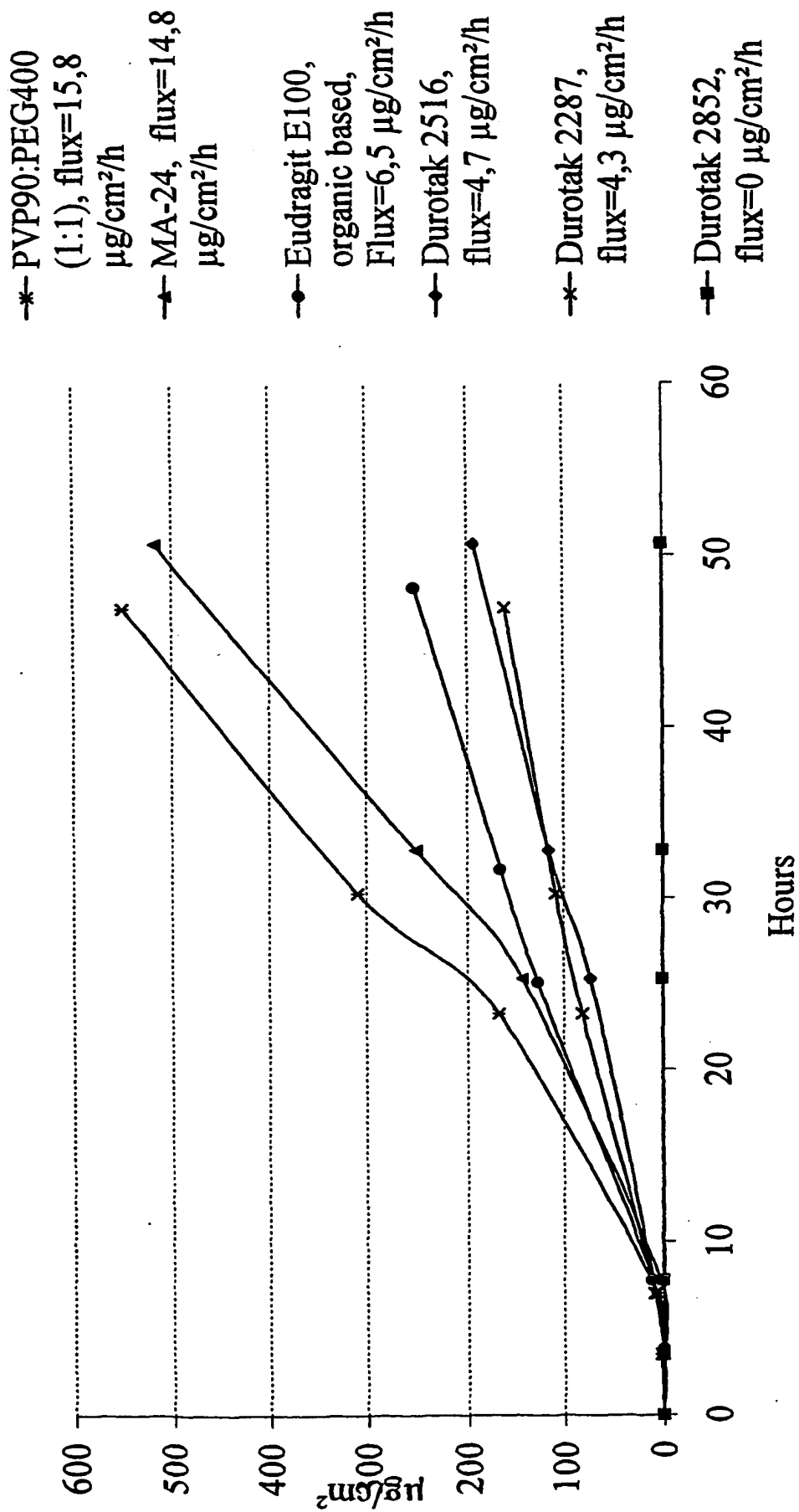


Figure 5

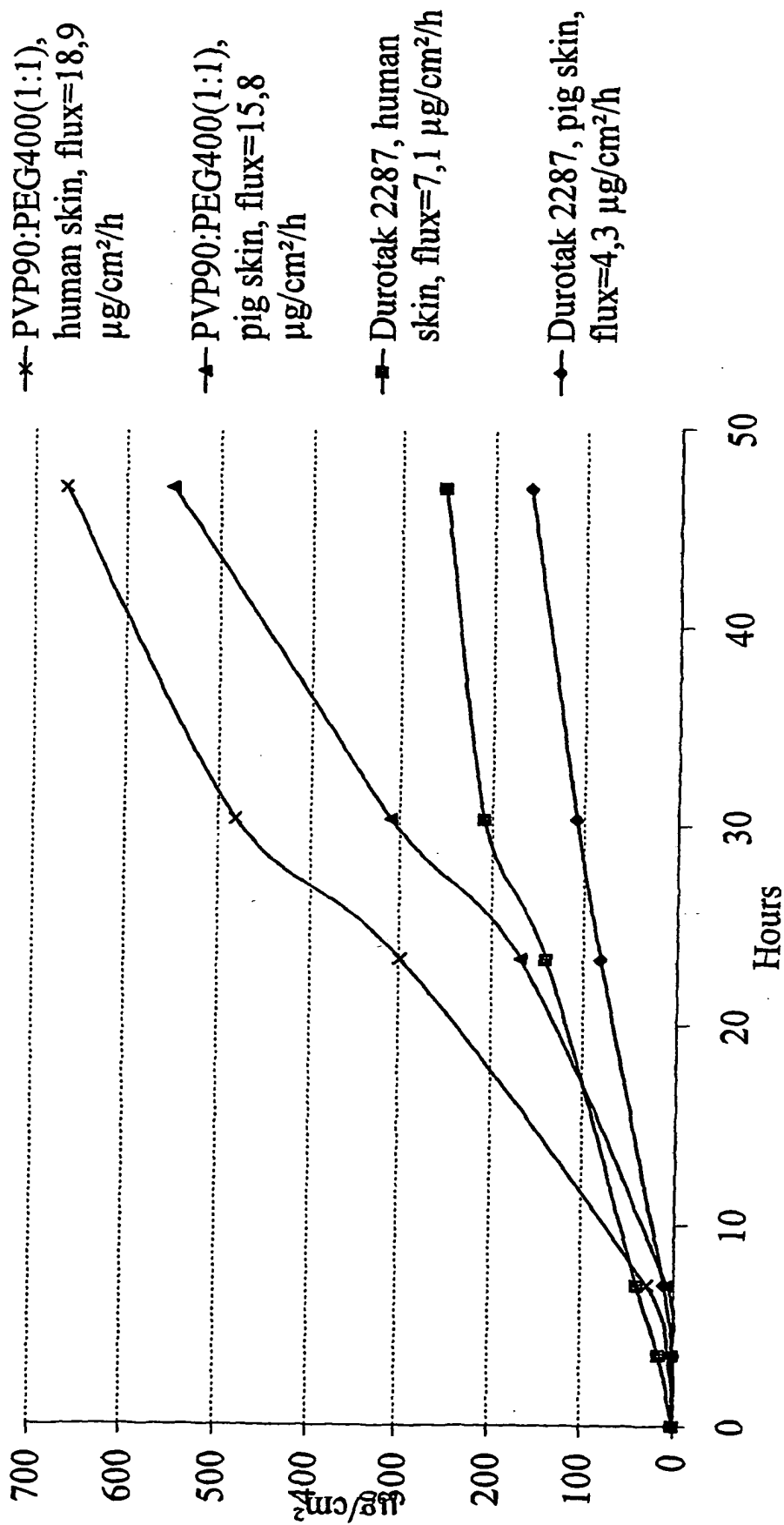


Figure 6

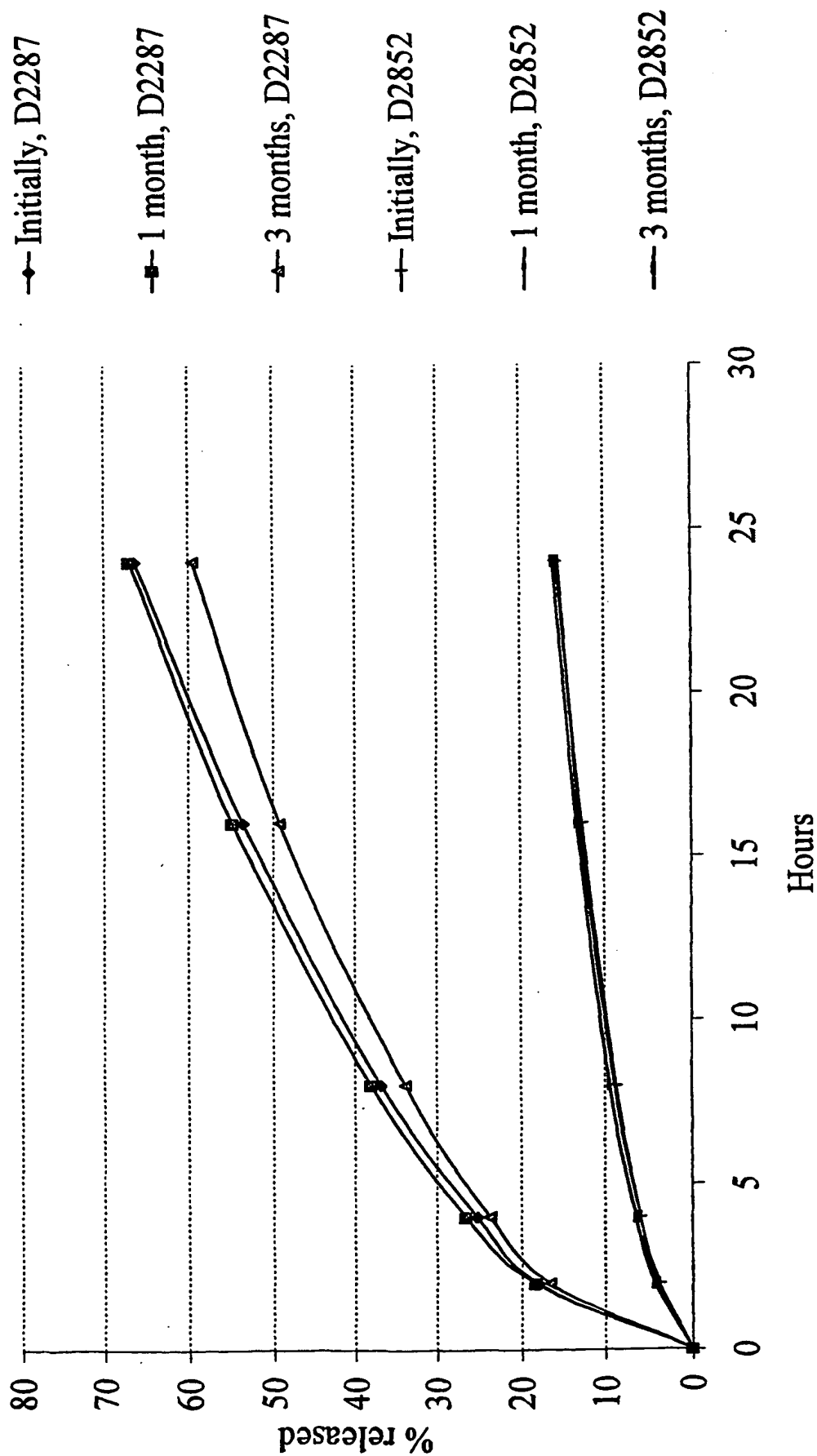


Figure 7

8/14

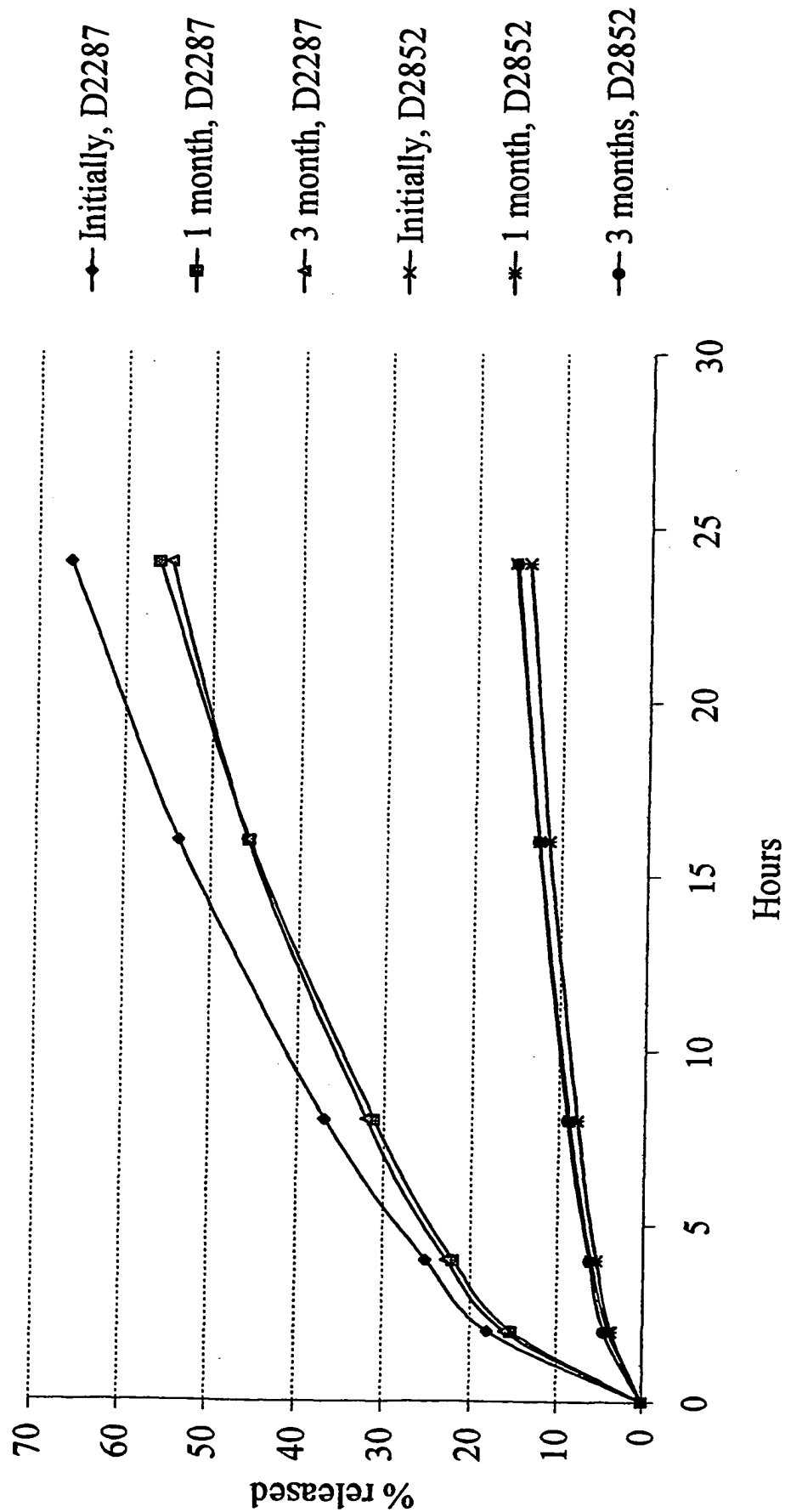


Figure 8

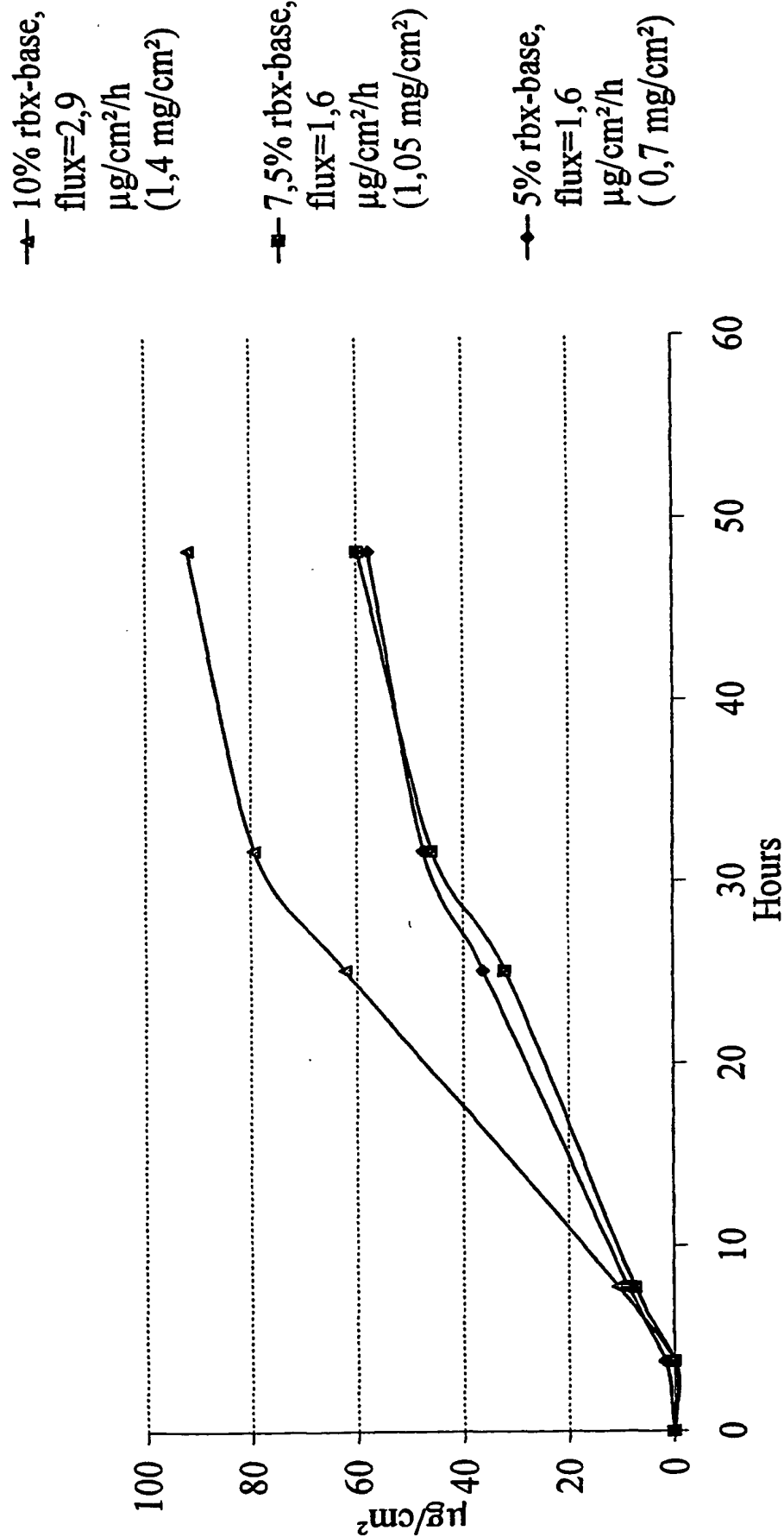


Figure 9

10/14

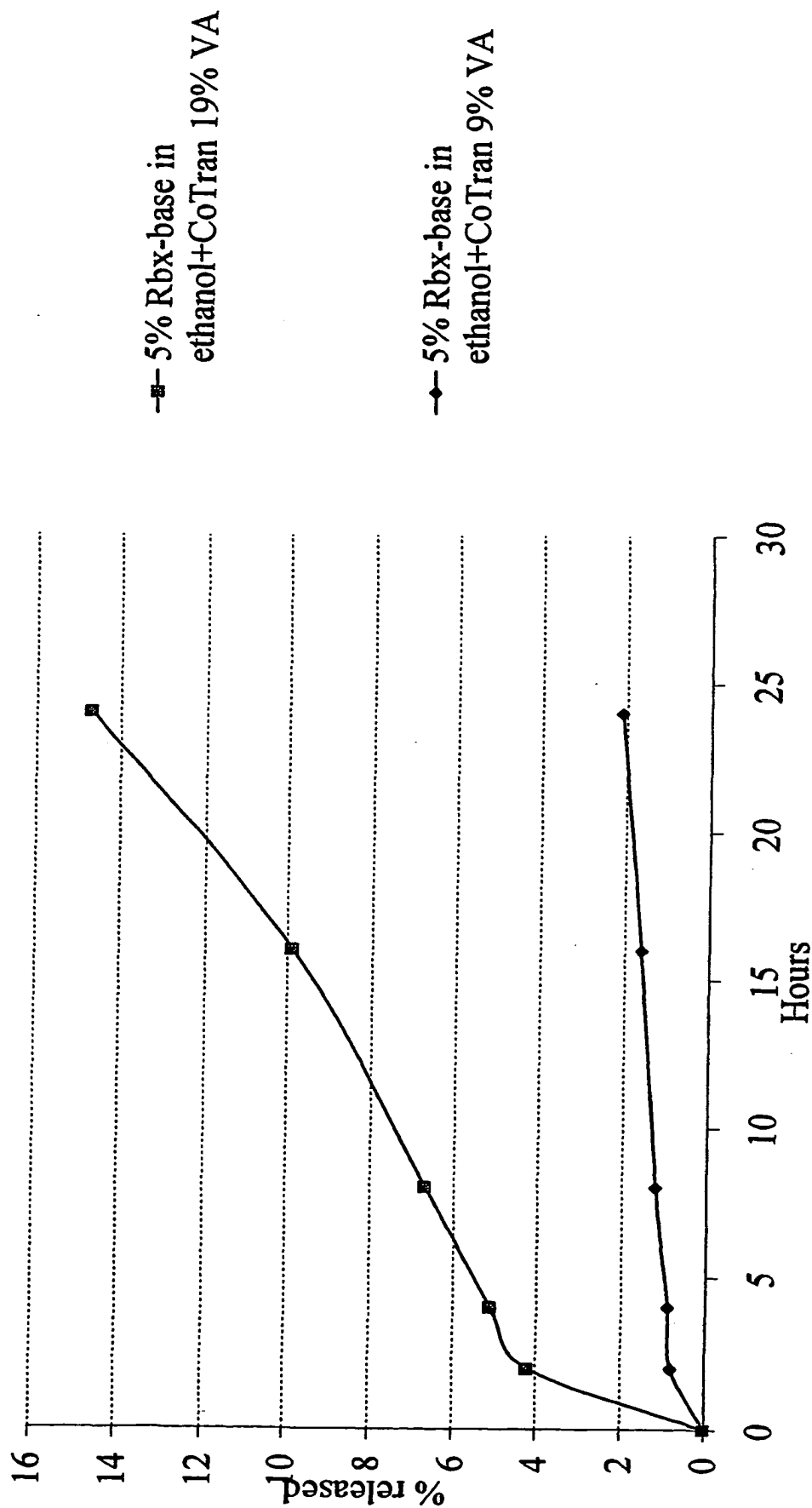


Figure 10



11/14

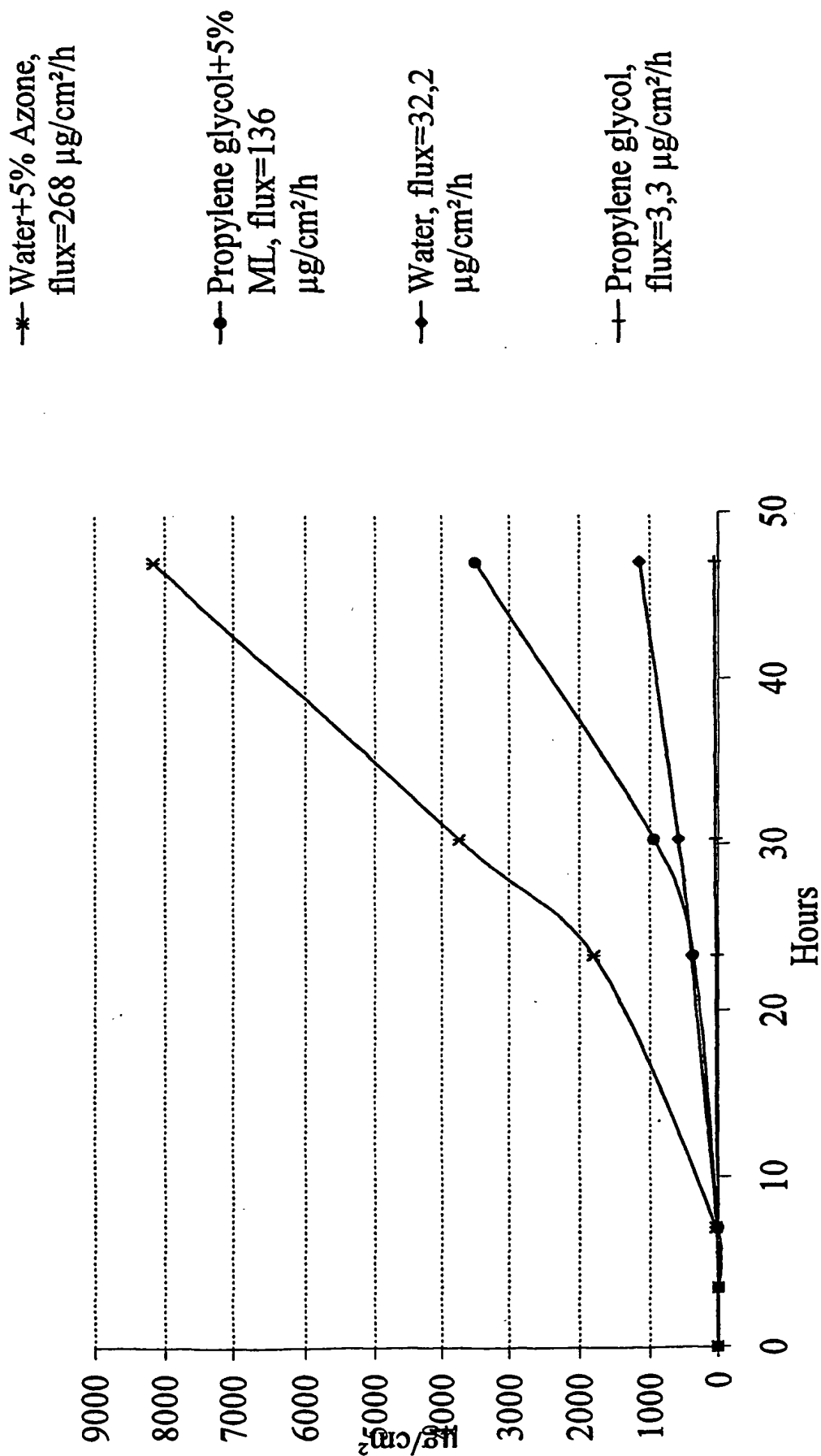


Figure 11

12/14

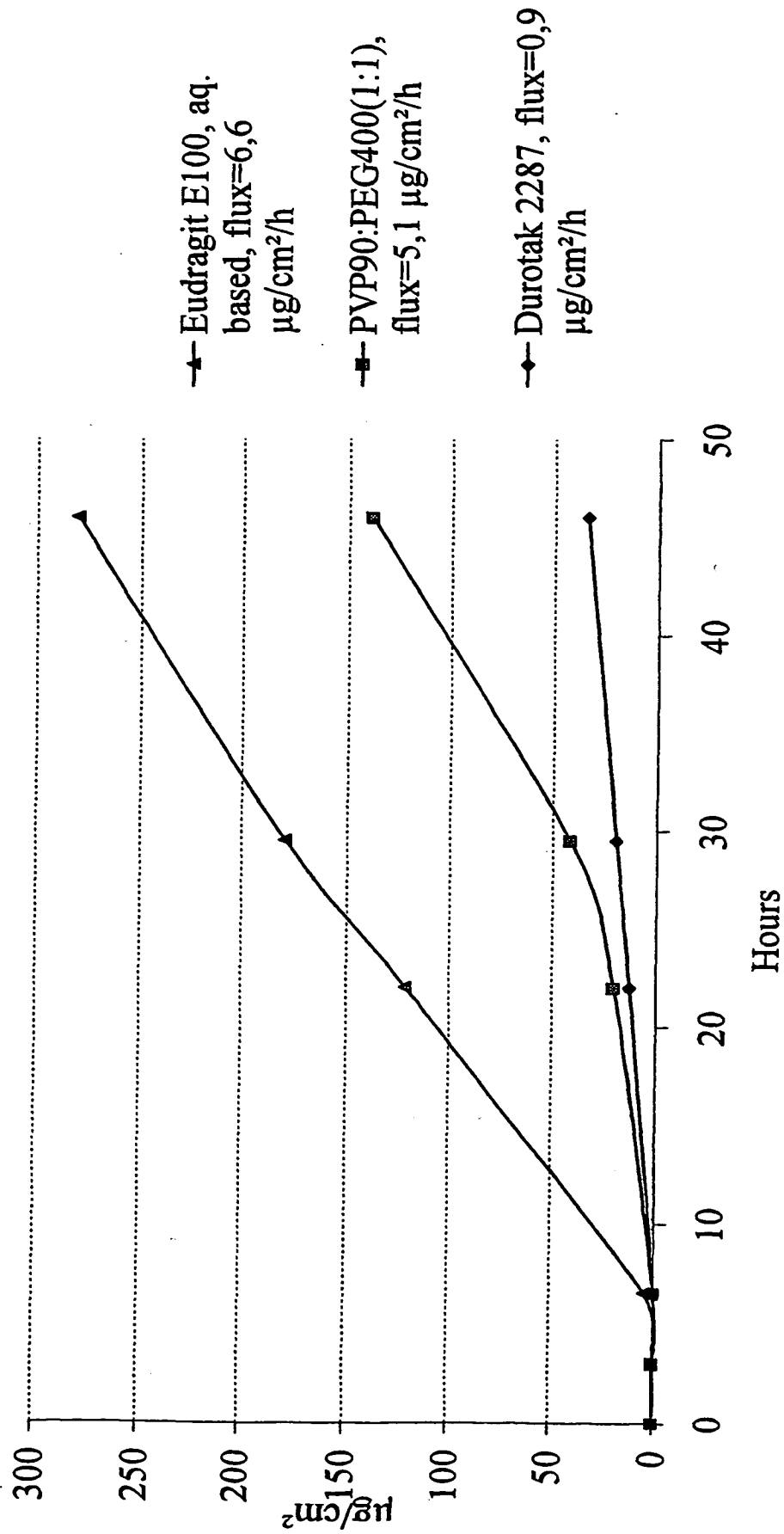


Figure 12

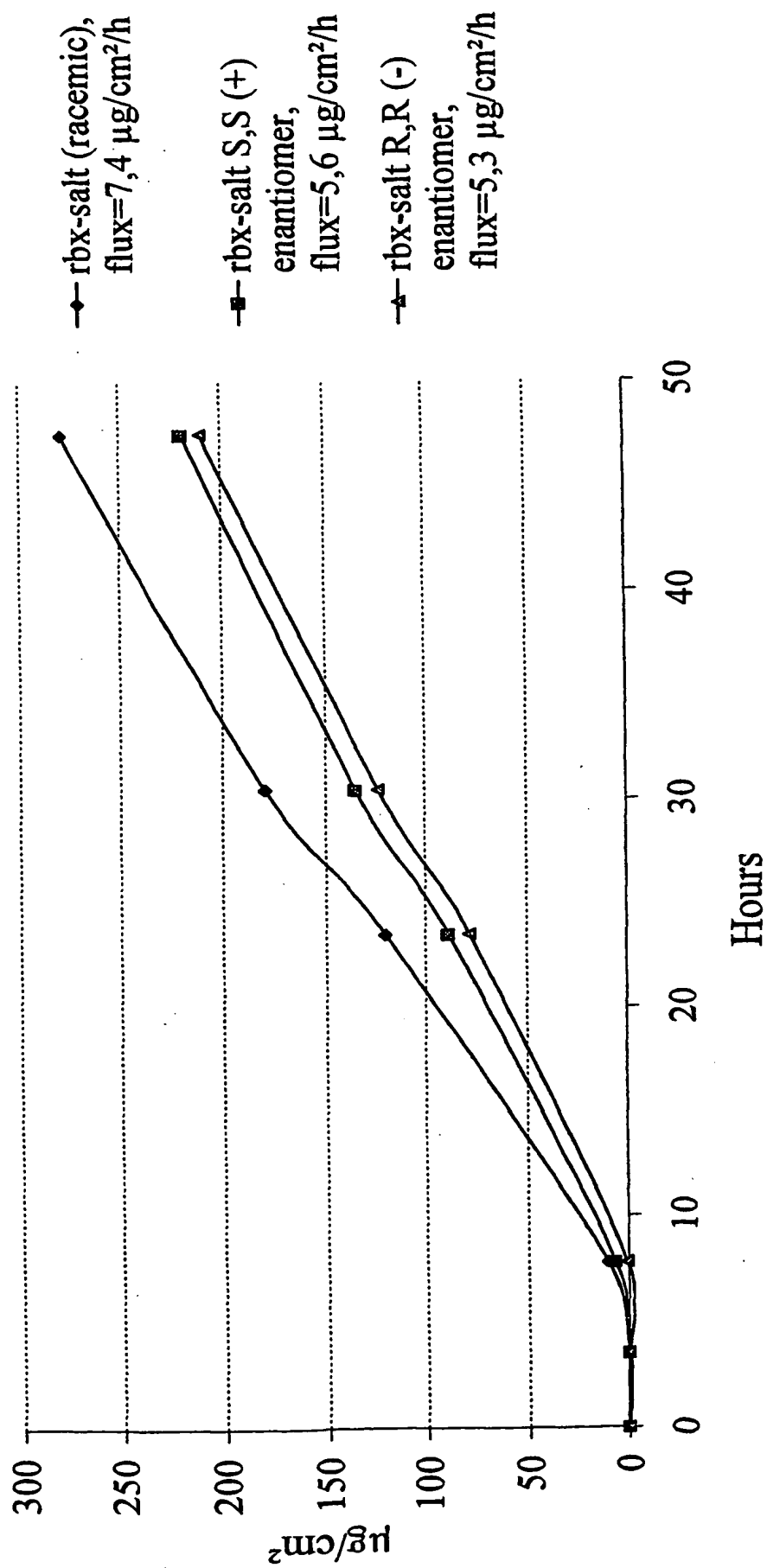


Figure 13

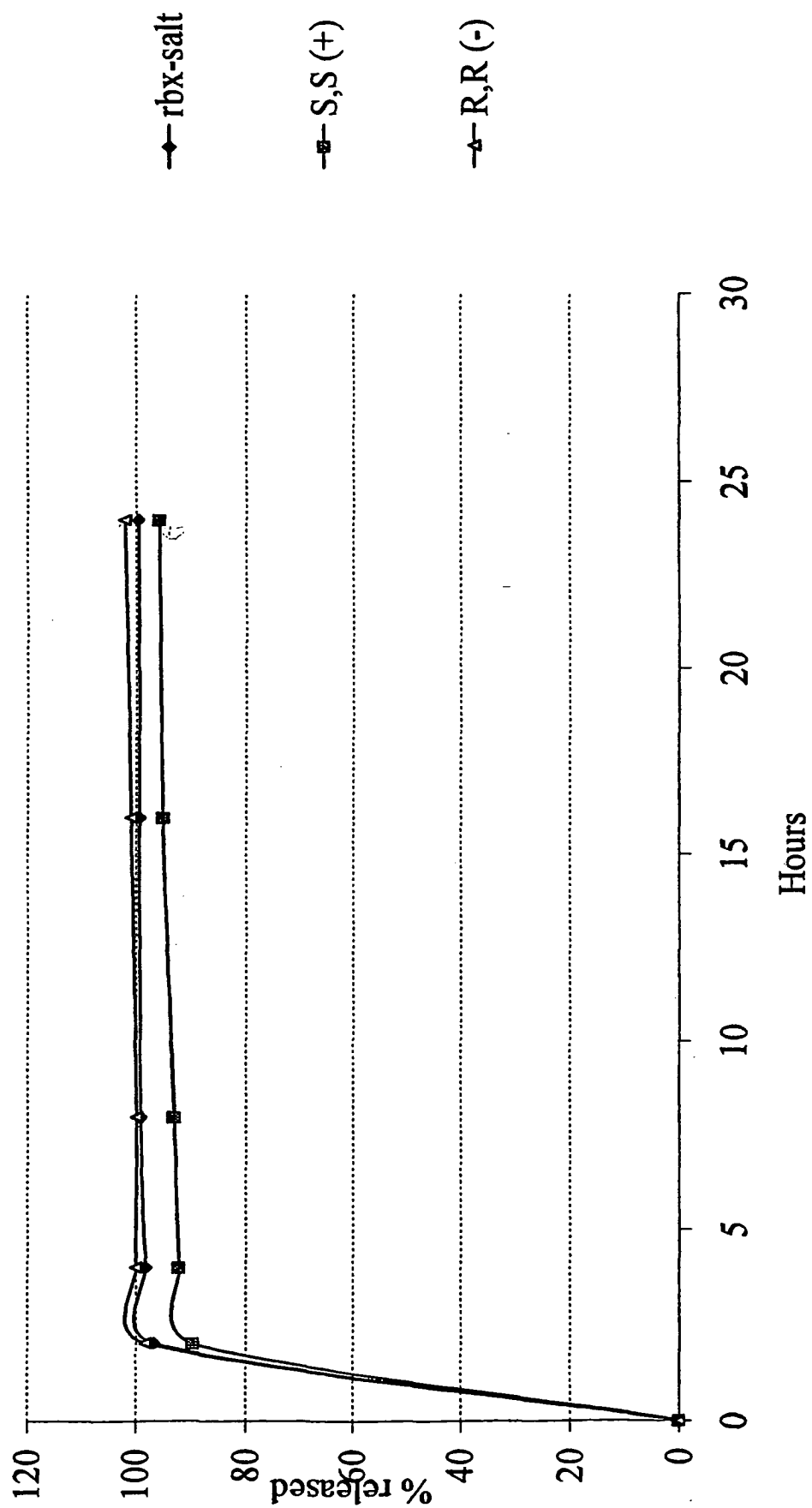


Figure 14

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 00/01972

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/70, A61K 31/5375, A61P 25/24  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9911208 A1 (WILLIAMS, C., DONALD), 11 March 1999 (11.03.99), see claim 32 and example 34  --	1-38
A	ADHESIVES AGE, September 1995, Steven M. Wick: "Developing A Drug-In-Adhesive Design For Transdermal Drug Delivery", page 18 - page 24  --	1-38
A	ADIS DRUG EVALUATION, Volume 12, No 1, July 1999, Kristin J. Holm et al, "Reboxetine. A Review of its Use in Depression" page 65 - page 83  -----	1-38

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
"E" earlier application or patent but published on or after the international filing date  
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 January 2001

Date of mailing of the international search report

29-01-2001

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Carolina Gómez Lagerlöf/Eö  
Telephone No. +46 8 782 25 00

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 00/01972

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **28-38**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 00/01972

Claims 28-38 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

27/12/00

International application No.

PCT/SE 00/01972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9911208 A1	11/03/99	AU 5155198 A	22/03/99

Form PCT/ISA/210 (patent family annex) (July 1998)